Global epidemiology of hepatitis A: implications for control strategies

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Worldwide, four patterns of hepatitis A virus (HAV) infection can be described based on age-specific prevalence of antibodies to HAV, which result in characteristic epidemiologic features. In areas of high endemicity, disease rates may be low because most infections occur in early childhood, when they are largely asymptomatic. With improvements in living conditions, a pattern of intermediate endemicity evolves, with high disease rates because of the sizeable cohort of susceptible persons likely to develop clinical manifestations with HAV infection. The epidemiology of hepatitis A is shifting in many highly endemic areas towards a pattern more consistent with intermediate endemicity, with resultant increases in disease burden. Marked variations in the degree of endemicity occur within countries and cities. Better information about hepatitis A epidemiology in these transitional areas will be needed to determine rational prevention strategies in the context of other national priorities. In areas of low and very low endemicity, the majority of the population remains susceptible throughout adulthood. In the USA, most hepatitis A occurs in the context of community-wide outbreaks, during which no risk factor is identified for 40–50% of cases. Epidemiologic data have been used to identify geographic areas in which the majority of disease occurs and where routine vaccination of children is recommended. Hepatitis A is now a vaccine preventable disease and the global disease burden will increase in coming years with shifts in age-specific prevalence occurring as living conditions improve. Epidemiologic data can be used to generate information for rational decision-making and to guide prevention and control programs

Introduction

In the almost 30 years since the causative agent of infectious hepatitis was identified and designated hepatitis A virus (HAV), much has been learned about its virology and epidemiology [1]. HAV is distributed worldwide, and is a classic example of an infectious disease in which the degree of endemicity is closely tied to the level of economic development and accompanying living conditions. Therefore, the epidemiology of hepatitis A changes with socioeconomic conditions, and the global status needs to be reassessed periodically. With the development of safe and effective hepatitis A vaccines in the early 1990s, understanding hepatitis A epidemiology has taken on new importance, because this information is needed to make well-informed decisions about prevention strategies and appropriate vaccine use.

Principles of hepatitis A epidemiology

Worldwide, four major patterns of HAV infection can be described based on the age-specific prevalence of antibodies to HAV (Figure 1). These range from high endemicity, such as in Africa and parts of Asia and Latin America, where the majority of infections occur in early childhood, to low and very low endemicity, such as in North America and Western Europe, where few persons are infected in childhood, and the majority of the population remains susceptible throughout adulthood [2–7].

An appreciation of the relationship between the age at infection and the clinical expression of disease is central to understanding hepatitis A epidemiology. The likelihood of having symptoms with HAV infection increases with the age at which infection occurs. In children <6 years of age, most infections are asymptomatic, and if symptoms do occur, they are usually mild and non-specific [8]. Among older children and adults, infection is usually symptomatic, with jaundice occurring in the majority of persons [9]. The disease tends to be more severe among older persons; among reported hepatitis A cases in the USA, the case fatality ratio increased from 0.2% among children 5–14 years old to 1.8% among adults >50 years old [10].

Because of the relationship between age at infection and clinical presentation, age-specific seroprevalence patterns result in characteristic features of hepatitis A epidemiology, including disease rates and predominant transmission patterns. In areas of high endemicity, disease rates may be low because most persons are infected at an age when infection is largely asymptomatic [11]. However, in some highly endemic areas disease rates may be high because of the high levels of circulating virus. For example, a population-based study conducted in the Amazon Basin of Brazil found the incidence of clinical disease among children to be over 100/100 000 population [12]. Transmission occurs primarily from person to person, but outbreaks from contaminated food or water also occur. In

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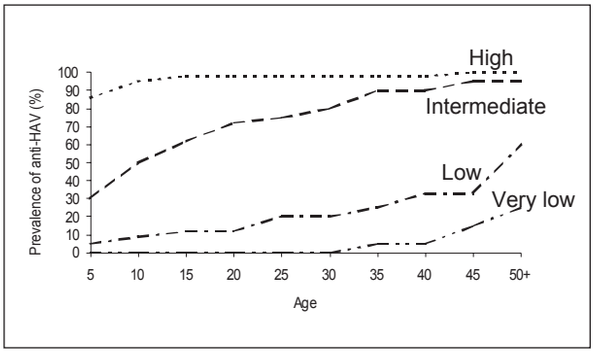
Figure 1. Patterns of hepatitis A virus infection worldwide



areas of intermediate endemicity, disease rates are high because high levels of virus circulate in a population that includes many susceptible older children, adolescents, and young adults, who are likely to develop clinical manifestations of HAV infection. Transmission from person to person can result in large epidemics; food and waterborne transmission can also occur. In areas of low endemicity, most older children, adolescents and young adults are susceptible, but disease rates are lower because of less opportunity for exposure to the virus. The predominant transmission pattern is from person to person, often in association with community-wide outbreaks; common source foodborne outbreaks are reported, but generally do not account for the majority of cases. In areas of very low endemicity, disease is often limited to adults in defined risk groups, such as international travelers and injection drug users.

Shifting global patterns

Because the level of hepatitis A endemicity is closely tied to the level of development, improvements in sanitary and living conditions and overall rises in socioeconomic status bring a shift in the age of infection to older age groups. This phenomenon, termed the 'epidemiologic shift', is manifested by a decrease in the age-specific prevalence of immunity to HAV and an increase in the pool of susceptible older children, adolescents, and young adults.

Important shifts in age-specific prevalence patterns that indicate a transition from high to intermediate endemicity are occurring in many parts of the world, including China, and countries in South America, Central and Southeast Asia, and the Middle East (Figure 2). Increases in the average age of infection have occurred, and in many areas anti-HAV prevalence among children is low [13–21]. These shifts can best be appreciated when prevalence is measured in the same population at two time points. For example, among 4000 Saudi children during 1989–1997, overall prevalence fell from 50 to 25%, and among children 9–10 years old from 68 to 34% (Figure 3) [14]. A similar downward shift in prevalence between 1987 and 1996 was observed among students in central Bangkok, where prevalence fell to 4% among 12–13 year old children (Figure 3) [22].

In some regions, these shifts have resulted in striking differences in anti-HAV prevalence among countries. A recent survey conducted in a number of Latin American countries documented a wide range of prevalence patterns among countries, from those typical of areas of high endemicity to patterns more consistent with intermediate endemicity [13]. In the Dominican Republic, 64% of

Figure 2. Geographic distribution of the prevalence of hepatitis A virus (based on summary of available data)

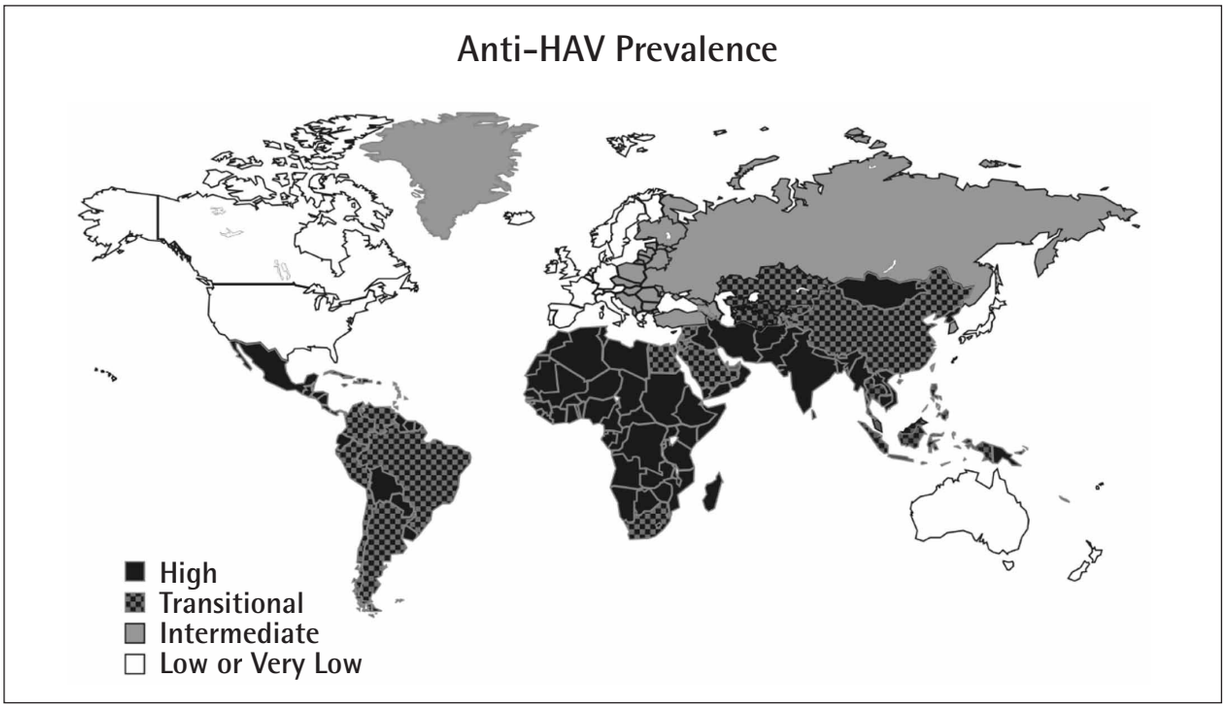
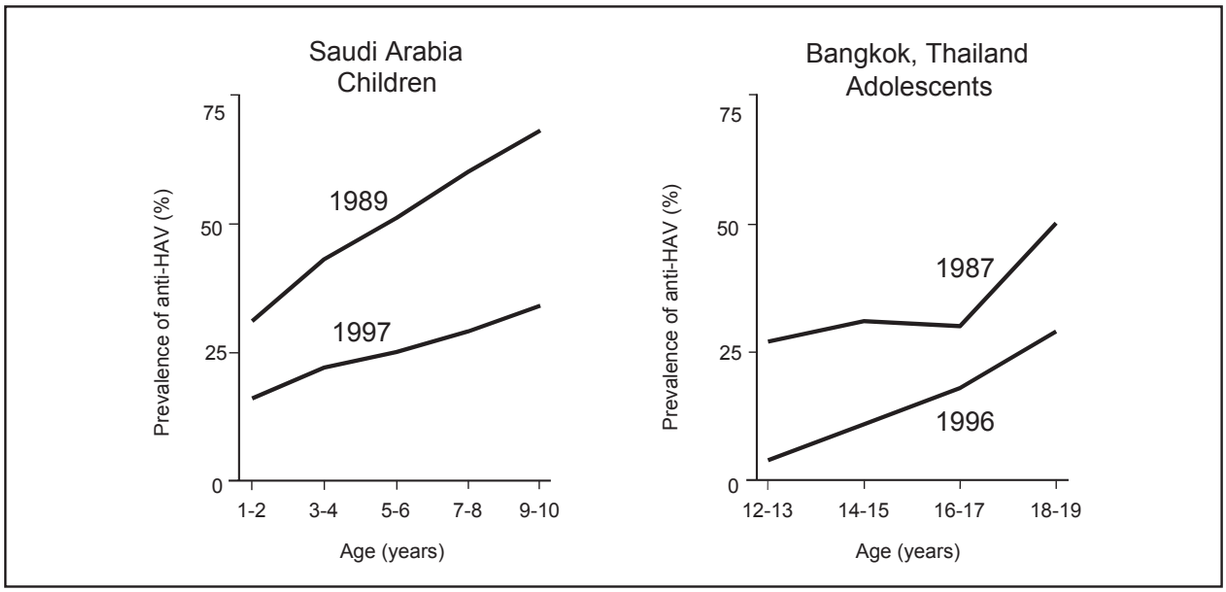


Figure 3. Changes in anti-HAV (antibody to hepatitis A virus) prevalence in two countries over one decade



children were immune to HAV by 5 years of age. In contrast, in Brazil, prevalence rose gradually with age, reaching 50% by early adolescence. In Chile, anti-HAV prevalence was only 31% among children up to age 10, and rose to 71% among adolescents, suggesting recent decreases in the incidence of infection.

Marked variations have been demonstrated within countries and cities [19,23–25]. A prevalence survey of persons 18–30 years, conducted in one medium-sized city in Brazil, found anti-HAV prevalence of 95% among persons of low socioeconomic status, compared to 20% among those of high socioeconomic status [25]. Similar differences in anti-HAV prevalence were seen between residents of urban and rural areas in a study of approximately 500 children in Riyadh, Saudi Arabia [19]. The overall prevalence of anti-HAV among those who had come from rural backgrounds was approximately 40%, compared to 25% among children from urban backgrounds.

Disease burden

The transition from high to intermediate endemicity can be expected to result in disease patterns characterized by increased morbidity, as cohorts of susceptible older children, adolescents, and adults become infected, and by a potential for outbreaks, as the susceptible population grows but relatively high levels of circulating virus persist. However, although studies from many parts of the world have documented shifting age-specific prevalence, little is known about current hepatitis A incidence and disease burden in most of the affected areas. Surveillance for viral hepatitis or jaundice is not routine, and sentinel networks or special studies are few. The World Health Organization no longer routinely collects information on the occurrence of viral hepatitis, and published disease burden estimates are based on incidence data from almost 20 years ago [26].

A few studies have documented the paradoxical rise in disease incidence with decreases in the age-specific prevalence of immunity. In Israel, hepatitis A incidence among children 5–14 years old doubled between 1951 and 1985, while incidence declined by approximately 50% among children aged 1–4 years [27]. In Egypt, where sentinel surveillance for acute viral hepatitis was conducted from 1995 to 1998 in four regions, the mean age of hepatitis A cases in Alexandria, an area of relatively high socioeconomic status, was 17.6 years, compared to 6.0 and 7.6 years in Cairo and the Nile Delta region, respectively, areas of lower socioeconomic status (F. Mahoney, Naval Medical Research Unit III, personal communication). During the 4-year study period, no hepatitis A cases were reported among children younger than 7 years old in Alexandria.

Large outbreaks have been documented in countries with transitional epidemiology. A classic example was the 1988 common source outbreak in Shanghai, associated with consumption of contaminated raw shellfish, which affected over 300 000 persons [28]. More recently, large outbreaks occurred in Central Asia in 1995–1997, with peak incidence rates of over 1000/100 000. In Tashkent, Uzbekistan, over 7000 cases were reported, resulting in overflowing hospitals and the closing of schools (MB Sharapov, Tashkent Pediatric Medical Institute, personal communication).

In some countries, cases of jaundice are counted, but not tested to determine the type of viral hepatitis. Thus, the 1995–1997 outbreak in Central Asia was initially assumed to be associated with hepatitis E virus, which is endemic in the region, but the age distribution of cases was different from that observed during previous hepatitis E outbreaks. Serologic testing of a sample of reported acute viral hepatitis cases indicated that the outbreak was due to HAV. Among 243 patients hospitalized with jaundice, 85% were anti-HAV positive, including virtually all cases among persons younger than 20 years. Although only a small number of cases occurred among persons 40 years and older, 50% were due to HAV (MB Sharapov, Tashkent Pediatric Medical Institute, personal communication).

Published case series illustrate the considerable hepatitis A-related morbidity and associated costs that can follow, even in the developing countries [29–34]. Hepatitis A is reported to account for 50–60% of all acute viral hepatitis cases among children in Pakistan, and 232 children with fulminant hepatic failure secondary to hepatitis A were admitted to one tertiary care referral hospital in Karachi during a 9-year period [32]. Hepatitis A was the etiology of the fulminant hepatitis of two-thirds of children presenting to two hospitals in Argentina during a 15-year period [34]. In one of these hospitals performing liver transplantations, one-third of liver transplantations among children were for fulminant hepatitis A.

Because surveillance is limited, little is known about current risk factors for hepatitis A in countries with transitional and intermediate endemicity. Most transmission is assumed to occur from person to person, but the role of specific exposures, such as child-care centers or schools, has not been determined. Although transmission from contaminated food and water occurs, the relative frequency of these exposures is unknown.

Hepatitis A epidemiology in the USA

In the USA, the majority of reported cases of acute viral hepatitis are due to hepatitis A [35]. Among vaccine preventable notifiable conditions, hepatitis A continues to be one of the most frequently reported; in 1997, over 30 000 cases of clinical hepatitis A were reported, and an estimated 90 000 occurred [10]. Catalytic models indicate that an estimated 270 000 HAV infections occurred each year during 1980-99 [36].

Most hepatitis A occurs in the context of community-wide outbreaks, during which infection is transmitted from person to person in households and extended family settings [37]. These outbreaks may recur in a predictable cyclic pattern. For example, in one typical US city, fully 70% of cases reported during a 15-year period occurred during two periods totaling 5 years, when community-wide outbreaks occurred [37]. During outbreaks, some groups at increased risk of hepatitis A can be identified, such as injection drug users or men who have sex with men. However, persons with identified risk factors do not account for the majority of cases, and no risk factor can be identified for 40–50% of cases.

HAV infection is common in children, and children play an important role in HAV transmission because they can transmit their often asymptomatic or unrecognized infection to susceptible adults. During 1980-99, an estimated 117 000 HAV infections per year occurred among children <5 years old, 43% of the estimated total [36]. In one study of adults without an identified source of infection, 40% of their household contacts <6 years old had serologic evidence of acute HAV infection, and the presence of a young child was associated with household transmission [38].

There is considerable regional variation in hepatitis A rates, with incidence being consistently higher in the western and southwestern USA compared to other regions (Figure 4). Among states, surveillance data demonstrate three general epidemiologic patterns (Figure 5). States can be identified in which disease incidence has been consistently elevated with respect to the national average, with peaks that were as much as nine times the national

Figure 4. Number of years reported hepatitis A incidence exceeded 10 cases per 100 000 population (approximately the US average rate), by county; 1987–1997

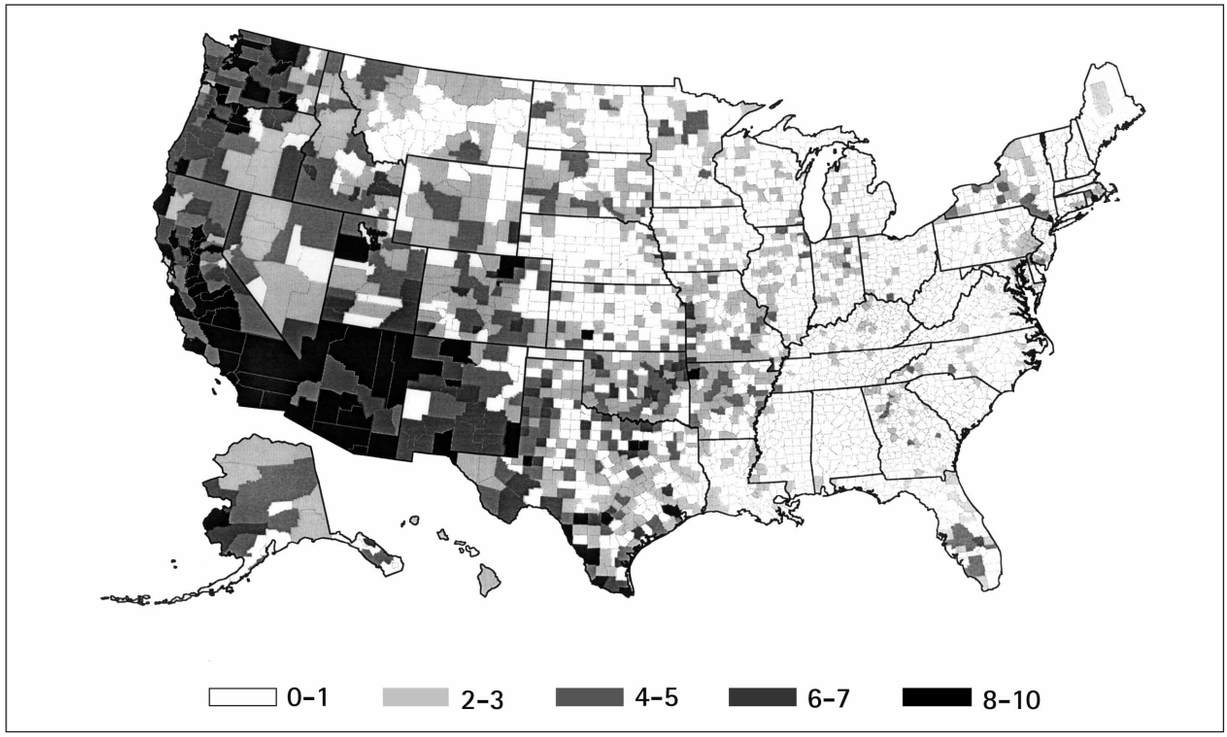
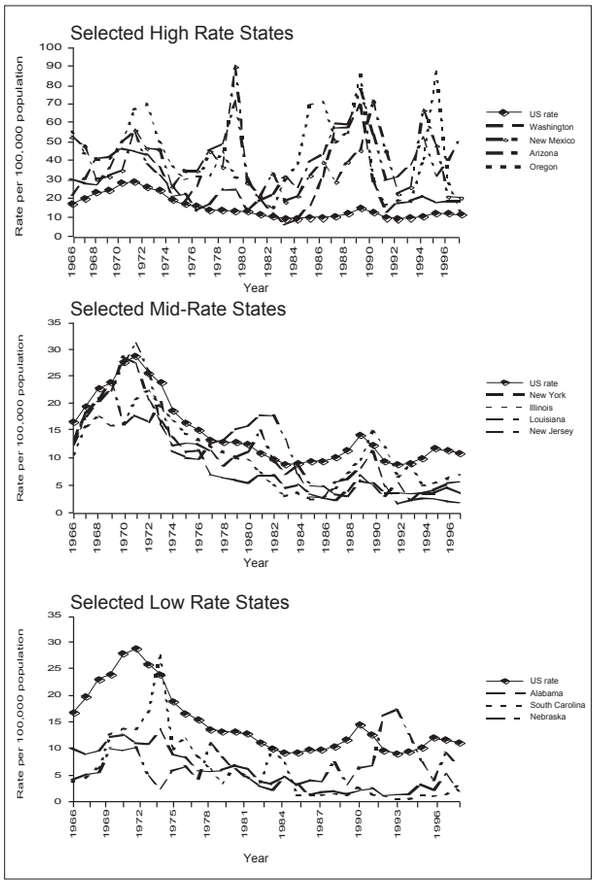


Figure 5. Incidence of hepatitis A, selected states with high, mid, and low hepatitis A rates, USA, 1966–1997



average. A second group of states have rates that consistently cluster around the national average, while in some states, hepatitis A incidence remains below the national average, even during peak incidence years.

The majority of hepatitis A cases nationwide are reported from states with consistently elevated rates. During 1987–1997, the 11 states with hepatitis A rates of at least 20 per 100 000, approximately twice the national average, reported an average of 50% of all reported cases, yet these states include only 22% of the US population [10]. An additional 18% of cases were from states with an average annual incidence above the national average during this time but less than twice the national average. In total, over two-thirds of reported cases occurred among residents of 17 states, encompassing approximately one-third of the US population. These areas with consistently elevated rates that contribute the majority of cases to the national disease burden provide a focus for routine childhood vaccination programs in the USA.

Conclusions

Hepatitis A is now a vaccine preventable disease, and decisions will need to be made about when and how the vaccine should be used. This will require a better understanding of the disease burden, areas or groups at highest risk, and transmission patterns. These epidemiologic data can be used to generate information for rational decision-making regarding prevention and control efforts.

The global disease burden associated with hepatitis A will increase in the coming years because of shifts in age-specific prevalence that have occurred with improvements in living conditions. These shifts already can be documented in many countries previously considered to be of high endemicity where disease burden was assumed to be low. Epidemiologic patterns in regions and countries are heterogeneous. By strengthening surveillance and making use of sentinel or other limited systems, the countries or parts of countries most affected by these shifts, where vaccination programs might be focused, can be identified.

Hepatitis A is now of transitional or intermediate endemicity in much of the world, and these areas are at risk for rising disease incidence and large outbreaks. In order to be prepared to respond in a rational and timely fashion, better information about the occurrence of hepatitis A and other types of viral hepatitis is needed. Updated estimates of disease burden at the country, regional and global levels need to be generated so that the cost-effectiveness of hepatitis A vaccination can be evaluated and compared to that of other public health priorities.

In areas of low endemicity, hepatitis A epidemiologic patterns are also complex, with considerable heterogeneity within countries. Existing public health surveillance systems can be used to characterize various patterns, identify areas or groups in which disease is concentrated, and guide the implementation of prevention programs.

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